REMARKS

Claims 227-234, 240, 243, and 248-262 are pending in this application. Claims 227-232, 234, 240 and 243 have been amended. Claims 248-262 are withdrawn. Withdrawn claims 248, 249, 252, 254, 255 and 259 have been amended in a manner consistent with the pending claims. New claim 263 is added herewith.

Support for the claim amendments and new claim can be found throughout the specification as filed. For example, support can be found at page 11, lines 12-22; page 13, lines 25-27; and page 15, lines 3-5.

35 U.S.C. § 101

Claims 227-234, 240 and 243 are rejected under 35 U.S.C. § 101, because the claims are allegedly directed to non-statutory subject matter. The Office contends that "[a] polypeptide containing a VH CDR1 and a VH CDR2 is not an art recognized term."

Solely in the interest of expediting prosecution, claim 227 and claims depending therefrom have been amended to recite the limitation "antibodies or functional fragments thereof". Applicants submit that the rejection under 35 U.S.C. § 101 is rendered moot by the amendments to the claims.

35 U.S.C. § 112, second paragraph

Claims 227-234, 240 and 243 are rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office alleges that one of ordinary skill in the art could not reasonably determine the metes and bounds the phrase "peptides, polypeptides or proteins each comprise a VH CDR1 and VH CDR2."

Solely in the interest of expediting prosecution, the terms "peptides, polypeptides or proteins" in the claims have been replaced with the terms "antibodies or functional fragments thereof". Applicants submit that the rejection under 35 U.S.C. § 112, second paragraph is rendered moot by the amendments to the claims.

35 U.S.C. § 103(a)

The Office Action has rejected claims 227-234, 240, and 243 as being obvious over Pini (*Jour. Biol. Chem.* 273:21769- 21776, 1998) in view of Stewart (*Jour. Exp. Med.* 177:409-418, 1993) and Yang (*Jour. Molec. Biol.* 254:392-403, 1995) as evidenced by Tomlinson (*Jour. Molec. Biol.* 227:776-798, 1992) and Brezinschek (*Jour. Clin. Invest.* 99:2488-2501, 1997).

As an initial matter, the Office states that "**claims 229 and 231-233** are product-by-process claims (sic) and the process recited in this claim is not given any patentable weight." (page 8, paragraph 3, lines 1-2 of the Office Action).

Applicants note that the terms "captured" and "isolated" have been removed from the claims. Claims 229 and 231-233, as amended, describe the composition itself and not the method of making it. Applicants submit that such claim amendments render this portion of the rejection moot.

Claims 227, 228, 230, 234, 240 and 243: The Office states

> Pini, Stewart and Yang are directed towards libraries of antibody peptides that include portions related to antibody regions VH CDR1 and VH CDR2 sequences. Pini and Stewart teach libraries that include polypeptides that include polypeptides that code for X_1-Y-X_2-M-X_3- in the VH CDR1 region and a VH CDR2 region that is almost identical to SEQ ID NO 637. Pini and Stewart teach in VH CDR2 X_4 and X_6 can be A, G or Y and X_6 can be G or S meeting the claim limitation of X_5 is Y, R, W, V, G or S and X_6 is P or S. One of ordinary skill in the art would have recognized the advantages of using the approach of varying X_4 and X_6 to other residues from known antibodies because Yang teaches that saturation mutagenesis of CDRs, including VH CDR2, can result in an improvement in antibody affinity (see Abstract). Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art.

Applicants respectfully disagree.

The claims, as amended, are directed to a library of antibodies or functional fragments thereof, each member of the library comprising a heavy chain CDR1 region that comprises a sequence of -X_1-Y-X_2-M-X_3 (SEQ ID NO. 636) and a heavy chain CDR2 region that comprises an amino acid sequence of X_4-I-X_5-X_6-S-G-G-X_7-T-X_8-Y-A-D-S-V-K-G (SEQ ID NO. 637), where each X is limited to a specific choice of amino acid residues recited in the claims. While X_1-X_3 of heavy chain CDR1 and X_4-X_8 of heavy chain CDR2 can vary according to the limitations of the claims, other positions of the heavy chain CDR1 and heavy chain CDR2 of the members of the library remain fixed. Thus, each of the members (i.e., antibodies or functional fragments thereof) will necessarily comprise the same fixed amino acid residues in these positions of heavy chain CDR1 (e.g., Y, M) and heavy chain CDR2 (e.g., I, SGG, T, and YADSVKG). Applicants also note that X_1-X_8 of the sequences recited in the claims vary by specific guidelines and are not randomly mutated to any amino acid. For example, X_6 is selected from the group of amino acids consisting of P and S. Thus, while some of the members of the library will vary from one another at positions within heavy chain CDR1 and heavy chain CDR2, they will vary only according to the guidelines provided by the claims.

It should be noted that the library covered by the claims is actually part of a commercially available library that has been used to identify multiple drug targets that are in various stages of clinical trials.

Pini et al., Stewart et al. and Yang et al. do not teach a library of antibodies or functional fragments thereof, where all of the members of the library retain certain fixed amino acids in the heavy chain CDR1 and heavy chain CDR 2 and where the members can vary from one another at other amino acid residues in the HC CDR1 and the HC CDR2 according to the guidelines recited in the claims. To illustrate the differences between the antibodies disclosed in the references cited by the Office and the currently claimed library, Applicants provide the following comparison of the antibody sequences of the heavy chain CDR2 regions disclosed for the antibodies described by Pini et al. and Stewart et al. and the heavy chain CDR2 sequence of the present claims. (The first row provides Kabat numbering for heavy chain CDR2; the second sets forth the amino acid

sequences of heavy chain CDR2 of the claimed library; the third row sets forth the amino acid sequence of heavy chain CDR2 of the library described by Pini et al[1]; the fourth row sets forth the amino acid sequence of the heavy chain CDR2 of the library described by Stewart et al).

50	51	52	52a	53	54	55	56	57	58	59	60	61	62	63	64	65
X_4 Y, R, W, V, G, S	I	X_5 Y, R, W, V, G, S	X_6 P, S	S	G	G	X_7 Any except C	T	X_8 Any except C	Y	A	D	S	V	K	G
A, S	I	S, R	G	S	G, S	G	S	T	Y	Y	A	D	S	V	K	G
A, G	I	S	G	S	G	G	S	T	Y	Y	A	D	S	V	K	G

As can be seen from the chart provided above, neither Pini et al., nor Stewart et al. teach or suggest a library having a heavy chain CDR2 that is fixed at certain amino acids according to the guidelines recited in the claims and that is variable between members at the other amino acid residues according to the guidelines provided in the claims.

There are several distinctions between the sequences described by Pini et al. and Stewart et al. and the claimed sequences. For example, Pini et al. and Stewart et al. disclose a library wherein the members are fixed at amino acid X_6 (position 52a) to have a glycine whereas the claimed library has variability to this position, with members having either a serine or proline. As another example, Pini et al. disclose a library that has variability at position 54 whereas the claimed library is fixed at that position. The libraries of Pini et al. and Stewart et al. also require that the amino acids at X_7 (position 56) and X_8 (position 58) are fixed whereas the claimed library allows variability at both of these positions. There is nothing in either Pini et al. or Stewart et al. which would teach or suggest a library that allows set variability at certain positions within heavy

[1] Part of the amino acid sequence described by Pini et al. was not disclosed in the Pini et al. reference. The amino acid residues for the positions not disclosed by Pini et al. were obtained from the nucleic acid sequence encoding DP47 as provided by Tomlinson et al.

chain CDR2 that the references disclose as fixed or that certain positions remain fixed at certain positions that the references disclose as variable.

In fact, Pini et al. teach away from using any set of guidelines for amino acid mutations and instead teach random mutations for the construction of a library. For example, Pini et al. state at page 21770, column 1, paragraph 3, lines 4-9:

> The VH component of the library was created using partially degenerate primers (Fig.1 and Table I) in a PCR-based method to introduce ***random*** mutations at positions 95-98 in CDR3. (Emphasis added)

It is clear from this statement that the library disclosed by Pini et al. was made using random mutations. See also, page 21770 of Pini et al. which discloses introducing random mutations into particular positions in heavy chain CDR1 and heavy chain CDR2. Nothing in this reference teaches or suggests a library of antibodies or antibody fragments having set guidelines for amino acids allowed at positions of variability between the members of the library at certain positions.

Stewart et al. disclose a library that has variability in heavy chain CDR1 and heavy chain CDR3 but not in heavy chain CDR2. Thus, there is nothing in this reference which would suggest to one of ordinary skill in the art to change the heavy chain CDR2 of Pini et al., much less to change it to require the guidelines set forth in the claims.

In addition, none of the remaining references cited by the Office, namely Yang et al., Tomlinson et al. and Brezinschek et al., provide any guidance for mutating certain amino acid residues within heavy chain CDR1 and heavy chain CDR2 while retaining other residues fixed as required by the presently claims. Further, none of these references teaches or suggests a library of antibodies or antibody fragments that have variability at certain positions within heavy chain CDR1 and heavy chain CDR2 according to the guidelines provided in the present claims.

For at least the reasons provided herein, none of the references cited by the Office alone, or in combination, teaches or suggests all of the elements of the library as presently claimed. There is simply no guidance in the references to suggest the particular

combination of amino acid residues recited in the claims that provide diversity between members of the library. Further, there is simply no guidance in the references to suggest the amino acids that remain fixed at certain positions within the members of the library as recited in the claims. Therefore, the claimed library is inventive and nonobvious over the references cited by the Office.

CONCLUSION

For at least the reasons stated above, Applicants respectfully submit that all examined claims are in condition for allowance, which action is expeditiously requested. Applicants do not concede any positions of the Office that are not expressly addressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. The Commissioner is hereby authorized to apply any necessary charges, or any credits, to Deposit Account No. 50/2762, with reference to Attorney Docket No. D2033-708931.

Respectfully submitted,

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